64. The medicament of Claim 15 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl; and the autoantigen is insulin.

65. The medicament of Claim 15 wherein the bisphosphonic acid and the autoantigen are present in a form for separate administration.

## REMARKS

### I. Status of the Application

Please cancel nonelected Claims 22-38, and 40-51 without prejudice for filing in a divisional application. Claims 15, 17, 18, and 19 are amended. Claims 52-65 are added. Claims 15-20, and 52-65 are pending.

Support for language added to amended claims and for added claims is found in the specification as follows: support for "a treatment enhancing amount of a first active when in combination with a second active" and for "a treatment enhancing amount of a second active when in combination with a first active" is found at page 3, lines 14-21, where the effect of the combination is cited as greatly promoted.

Support for allergens "pollen, nickel, and food" is found at page 1, lines 16-18. Support for "myelin basic protein" is found at pages 10, 17, 18, and 19. Support for the bisphosphonic acids of Claims 58-64 is found at page 9, line 10 to page 10, line 2. Support for "present in a form for separate administration" is found at page 6, lines 28-30, and at page 14, lines 28-30.

### II. Rejection of Claims 15-18 under 35 USC §112, First Paragraph

#### Office Action

The Office Action states a rejection of Claims 15-17 for lack of enablement of language 'fragments or derivatives of autoantigens or allegens having the same immunological characteristic ...'. Undue experimentation was cited as needed to practice the claimed invention. Claim 18 (sic, 19) was rejected for containing new matter.

#### Response

Claims 15 and 17 have been rewritten to recite the second active ingredient as an autoantigen ingredient cited as enabled by the Office Action and as recited in previous Claim 18. Claims 52 and 53 have been added to recite the second active ingredient as an allergen ingredient as cited in the specification at page 1, lines 17-18. Claim 16 is dependent upon Claim 15. Claim 18 was inadvertently cited by the Action for containing new matter, while such alleged new matter is present in Claim 19. Claim 19 has been amended to be dependent upon Claim 52 and to recite pollen.

The amendments are believed to obviate the enablement rejections, and Applicant respectfully requests withdrawal of the rejections.

## III. Rejection of Claims 15-17 and 20 under 35 USC §102(b)

**Office Action**

The Office Action states a rejection of Claims 15-17 and 20 as being anticipated by Mundy. Mundy was cited as teaching bisphosphonates and "antigenic fragment" such as those at page 7, lines 23-27, page 13, lines 1-10 and Claims 1 and 6-8.

**Response**

For a prior art reference to anticipate, every element of the claimed invention must be identically shown in a single reference. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). Mundy's composition is not to the "antigenic fragment" cited by the Office Action but is to the antibody immunoreactive and immunospecific for such "antigenic fragment." Therefore, an element of the claimed invention that is missing from Mundy is the autoantigen or allergen of the present claims. Further support for this position is provided by a statement in the International Preliminary Examination Report for the priority application, PCT/DE99/01844 (submitted to the Patent Office March 9, 2001) at 2.2, "(WO 96/22790) is not relevant to the subjects of the present claims ... because the antibodies mentioned do not fall within the normal meaning and scope of the terms antigens or allergens ... ". Applicant therefore respectfully requests that the rejection be withdrawn.

## IV. Rejection of Claims 15-20 under 35 USC §103(a)

**Office Action**

The Office Action states a rejection of Claims 15-20 as being unpatentable over Lyons in view of Michael. The Action states that the references in combination make clear that bisphosphonic acids and protein antigens or allergens have been individually used for the treatment of autoimmune diseases, that the idea of combining them flows logically, and that the combination is merely the additive effect of each individual component.

**Response**

This rejection is respectfully traversed. The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. *In re Grabiak,* 226 USPQ 870 (Fed. Cir. 1985). Applicant submits that no such support is found in Lyons, or Michael or a combination thereof for the invention as claimed for a medicament that contains treatment enhancing amounts of the bisphosphonic acid and autoantigen or allergan when in combination.

It is respectfully requested that this rejection be withdrawn.

## V. Rejection of Claims 15-17 under 35 USC 103(a)

**Office Action**

The Office Action states a rejection of Claims 15-17 as being unpatentable over Ogawa which is cited as teaching a combination of activin and bisphosphonates.

**Response**

This rejection is respectfully traversed. The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. *In re Grabiak,* 226 USPQ 870 (Fed. Cir. 1985). Applicant submits that no such support is found in Ogawa for the invention as claimed. There is no teaching or suggestion in Ogawa that activin is an autoantigen or an allergen.

It is respectfully requested that this rejection be withdrawn.

## VI. Supplemental Information Disclosure Statements

A Supplemental Information Disclosure Statement was mailed to the Patent Office October 15, 2002. A further Supplemental Information Disclosure Statement is filed concurrently herewith. Applicant respectfully requests that the references cited therein are made of record and that a copy of the marked-up PTO-1449 forms be returned to Applicant.

## VII. Conclusion

In light of the foregoing amendments and remarks, it is believed that all matters set forth in the Office Action have been addressed. Reconsideration is respectfully requested. Should the Examiner have any questions, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Gloria L. Norberg

Dated: January 24, 2003

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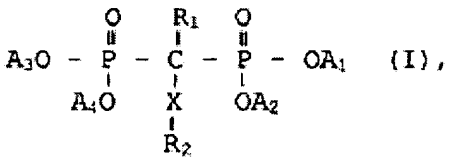
**MARKED UP VERSION OF THE CLAIMS**

15. (2X Amended) A medicament for treating an autoimmune disease[ or allergy], comprising a treatment enhancing amount of a first active ingredient when in combination with a second active ingredient, wherein the first active ingredient is selected from the group consisting of bisphosphonic acids corresponding to general formula (I)



(I),

in which

$A_1$, $A_2$, $A_3$ and $A_4$ are independently selected from the group consisting of

hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residues, metals of Groups I, II and III of the Periodic Table of the elements, and substituted and unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group consisting of alkylene, alkenylene and hydroxyalkylene,

$R_1$ and $R_2$ are independently selected from the group consisting of

H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residues, $-SR_3$, C1 and $-NR_3R_4$,

in which

$R_3$ and $R_4$ are independently selected from the group consisting of

H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic residues,

their pharmaceutically compatible salts, esters thereof, salts of the esters and compounds, which upon administration from the compounds according to formula (I) or their salts or esters as metabolites or catabolites,

and a treatment enhancing amount of a second active ingredient when in combination with the first active ingredient, wherein said second active ingredient is [selected from the group

consisting of an autoantigen ingredient and an allergen ingredient, wherein said autoantigen ingredient is selected from the group consisting of]

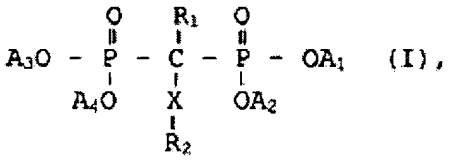
at least one autoantigen specific for the autoimmune disease to be treated and selected from the group consisting of nervous system tissue extracts, collagen, thyroglobulin, acetylcholine receptor protein, DNA, islet cell extracts, human insulin, liver extracts, adrenal cortex extracts, skin extracts, muscle extracts, haemopoetic cell line extracts, heart extracts, eye lens proteins, S-antigens, gastric cell extracts, parietal cell extracts, intrinsic factor, and intestinal extracts [, fragments of said autoantigens having the same immunological characteristics as said autoantigens, and derivatives of said autoantigens having the same immunological characteristics as said autoantigens,

and wherein said allergen ingredient is selected from the group consisting of

allergens specific for the allergy to be treated, fragments of said allergens having the same immunological characteristics as said allergens, and derivatives of said allergens having the same immunological characteristics as said allergens]; and

an excipient.

17. (2x Amended) A medicament for treating an autoimmune disease [or allergy], comprising a treatment enhancing amount of a first active ingredient when in combination with a second active ingredient, wherein the first active ingredient is selected from the group consisting of bisphosphonic acids corresponding to general formula (I)



(I),

in which

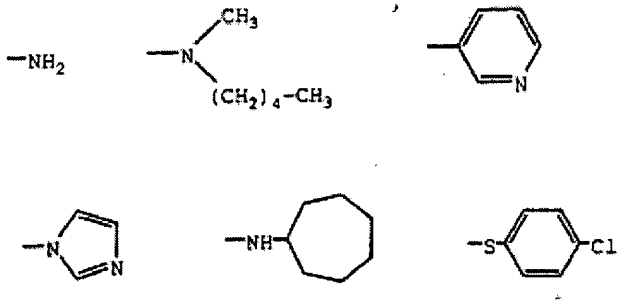
$A_1$, $A_2$, $A_3$ and $A_4$ are independently selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residues, metals of Groups I, II and III of the Periodic Table of the elements, and substituted and unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group consisting of $(CH_2)_{1-5}$ and amidino,

$R_1$ is selected from the group consisting of

H and OH, and

$R_2$ is selected from the group consisting of




their pharmaceutically compatible salts, esters thereof, salts of the esters and compounds, which upon administration form the compounds according to formula (I) or their salts or esters as metabolites or catabolites,

and a treatment enhancing amount of a second active ingredient when in combination with the first active ingredient, wherein said second active ingredient is [selected from the group consisting of an autoantigen ingredient and an allergen ingredient, wherein said autoantigen ingredient is selected from the group consisting of]

at least one autoantigen specific for the autoimmune disease to be treated and selected from the group consisting of nervous system tissue extracts, collagen, thyroglobulin, acetylcholine receptor protein, DNA, islet cell extracts, human insulin, liver extracts, adrenal cortex extracts, skin extracts, muscle extracts, haemopoetic cell line extracts, heart extracts, eye lens proteins, S-antigens, gastric cell extracts, parietal cell extracts, intrinsic factor, and intestinal extracts [, fragments of said autoantigens having the same immunological characteristics as said autoantigens, and derivatives of said autoantigens having the same immunological characteristics as said autoantigens,

and wherein said allergen ingredient is selected from the group consisting of

allergens specific for the allergy to be treated, fragments of said allergens having the same immunological characteristics as said allergens, and derivatives of said allergens having the same immunological characteristics as said allergens]; and

an excipient.

18. (2x Amended) The medicament of claim 15, wherein the autoantigen is selected from the group consisting of nervous system tissue extracts, [collagen, thyroglobulin, acetylcholine receptor protein, DNA,] islet cell extracts, [human insulin,] liver extracts, adrenal cortex extracts, skin

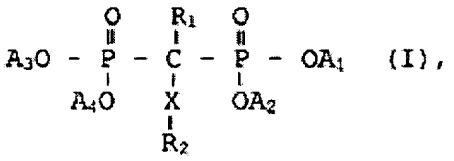
extracts, muscle extracts, haemopoetic cell line extracts, heart extracts, [eye lens proteins, S-antigens,] gastric cell extracts, parietal cell extracts, [intrinsic factor,] and intestinal extracts.

19. (Amended) The medicament of claim 52 [15], wherein the allergen is [selected from the group consisting of] pollen[, dust, mites, foods, animal danders, and insect venom].

Please add Claims 52-65 as follows.

--52. A medicament for treating an allergy, comprising:

a treatment enhancing amount of a first active ingredient when in combination with a second active ingredient, wherein the first active ingredient is selected from the group consisting of bisphosphonic acids corresponding to general formula (I)



(I),

in which

$A_1$, $A_2$, $A_3$ and $A_4$ are independently selected from the group consisting of

hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residues, metals of Groups I, II and III of the Periodic Table of the elements, and substituted and unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group consisting of alkylene, alkenylene and hydroxyalkylene,

$R_1$ and $R_2$ are independently selected from the group consisting of

H, OH, $-NH_2$, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heterocyclic residues, $-SR_3$, C1 and $-NR_3R_4$,

in which

$R_3$ and $R_4$ are independently selected from the group consisting of

H, OH, substituted and unsubstituted acyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl and substituted and unsubstituted heterocyclic residues,

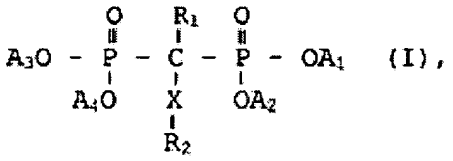
their pharmaceutically compatible salts, esters thereof, salts of the esters and compounds, which upon administration from the compounds according to formula (I) or their salts or esters as metabolites or catabolites,

and a treatment enhancing amount of a second active ingredient when in combination with the first active ingredient, wherein said second active ingredient is an allergen ingredient specific for the allergy to be treated and is selected from the group consisting of pollen, nickel, and food; and

an excipient.

53. A medicament for treating an allergy, comprising:

a treatment enhancing amount of a first active ingredient when in combination with a second active ingredient, wherein the first active ingredient is selected from the group consisting of bisphosphonic acids corresponding to general formula (I)



(I),

in which

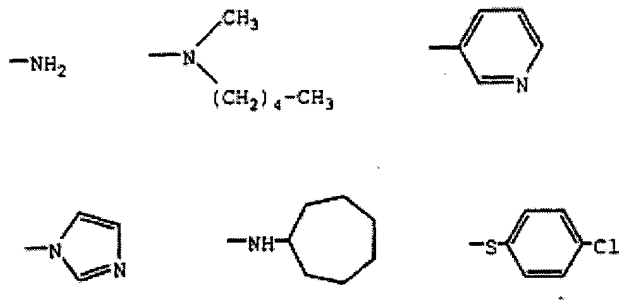
$A_1$, $A_2$, $A_3$ and $A_4$ are independently selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, substituted and unsubstituted aryl, substituted and unsubstituted aralkyl, substituted and unsubstituted cycloalkyl, substituted and unsubstituted heterocyclic residues, metals of Groups I, II and III of the Periodic Table of the elements, and substituted and unsubstituted ammonium or ammonium compounds derived from ethylenediamine or amino acids,

X is absent or is selected from the group consisting of $(CH_2)_{1-5}$ and amidino,

$R_1$ is selected from the group consisting of

H and OH, and

$R_2$ is selected from the group consisting of



their pharmaceutically compatible salts, esters thereof, salts of the esters and compounds, which upon administration form the compounds according to formula (I) or their salts or esters as metabolites or catabolites,

and a treatment enhancing amount of a second active ingredient when in combination with the first active ingredient, wherein said second active ingredient is an allergen ingredient specific for the allergy to be treated and selected from the group consisting of pollen, nickel, and food; and

an excipient.

54. The medicament of claim 15, wherein the autoantigen is from a nervous system tissue extract and the autoantigen is myelin basic protein.

55. The medicament of claim 15, wherein the autoantigen is selected from the group consisting of collagen, thyroglobulin, acetylcholine receptor protein, human insulin, eye lens proteins, S-antigens, and intrinsic factor.

56. The medicament of claim 15, wherein the autoantigen is DNA.

57. The medicament of Claim 52, wherein the allergen ingredient is food.

58. The medicament of Claim 15 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl.

59. The medicament of Claim 15 wherein the bisphosphonic acid is amidinomethylenebisphosphonic acid, ibandronic acid, risedronic acid, zoledronic acid, cimadronic acid, or tiludronic acid.

60. The medicament of Claim 52 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl.

61. The medicament of Claim 52 wherein the bisphosphonic acid is amidinomethylenebisphosphonic acid, ibandronic acid, risedronic acid, zoledronic acid, cimadronic acid, or tiludronic acid.

62. The medicament of Claim 15 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl; and the autoantigen is from a nervous system tissue extract and is myelin basic protein.

63. The medicament of Claim 15 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl; and the autoantigen is collagen.

64. The medicament of Claim 15 wherein the bisphosphonic acid is an amino-1-hydroxyalkylidene-1,1-bisphosphonic acid wherein the alkyl is methyl, ethyl, propyl, butyl, or hexyl; and the autoantigen is insulin.

65. The medicament of Claim 15 wherein the bisphosphonic acid and the autoantigen are present in a form for separate administration.--